PATENT
034827-0302

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re the Application of:

Richard W. Tseng & Michael K. Samoszuk

Serial No.: 09/747,165

Title: BCR-ABL GENE REARRANGEMENT ASSAY METHOD

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Group Art Unit: 1637

Examiner: Jeffrey Norman Fredman

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APPEAL BRIEF

Commissioner for Patents
Washington, D.C. 20231

Sir:

Applicant (herein, "Appellant") hereby appeals the Final Rejection of claims 1-13. This Appeal Brief is accompanied by the requisite fee of $320.00 as set forth in 37 C.F.R. § 1.17(f). If this fee is incorrect or if any additional fees are due in this regard, please charge or credit our Deposit Account No. 50-0872 for the appropriate amount.

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Real Party in Interest

The real party in interest in this appeal is Quest Diagnostics Investments, Inc., which is the assignee of the present application.

Related Appeals and Interferences

Appellants are not aware of any related appeals or interferences that may have a bearing on the board's decision in the pending appeal.

Status of Claims

On November 7, 2002, Appellants appealed from the Examiner's Action of August 7, 2002, making final the rejection of claims 1-13. Claims 2 and 3 stand finally rejected under 35 U.S.C. 112, second paragraph. Claims 1-6 and 8-13 stand finally rejected under 35 U.S.C. §103(a) as allegedly being unpatentable over Mensink *et al.* in view of Hariharan *et al.* and further in view of Shtivelman. Claims 1-13 stand finally rejected under 35 U.S.C. 103(a) as allegedly being unpatentable over Eder *et al.* in view of Hariharan *et al.* and further in view of Shtivelman and further in view of Ercolani *et al.*

Status of Amendments

On November 7, 2002, Appellants submitted a response under 37 C.F.R. §1.116 to the Examiner's Action of August 7, 2002. Five days later, Appellants submitted a Supplemental Response, including copies of several publications referred to, but inadvertently not included, in Appellants' November 7, 2002 response. In an Advisory Action dated November 22, 2002, the Examiner indicated that the cited publications were not being considered.

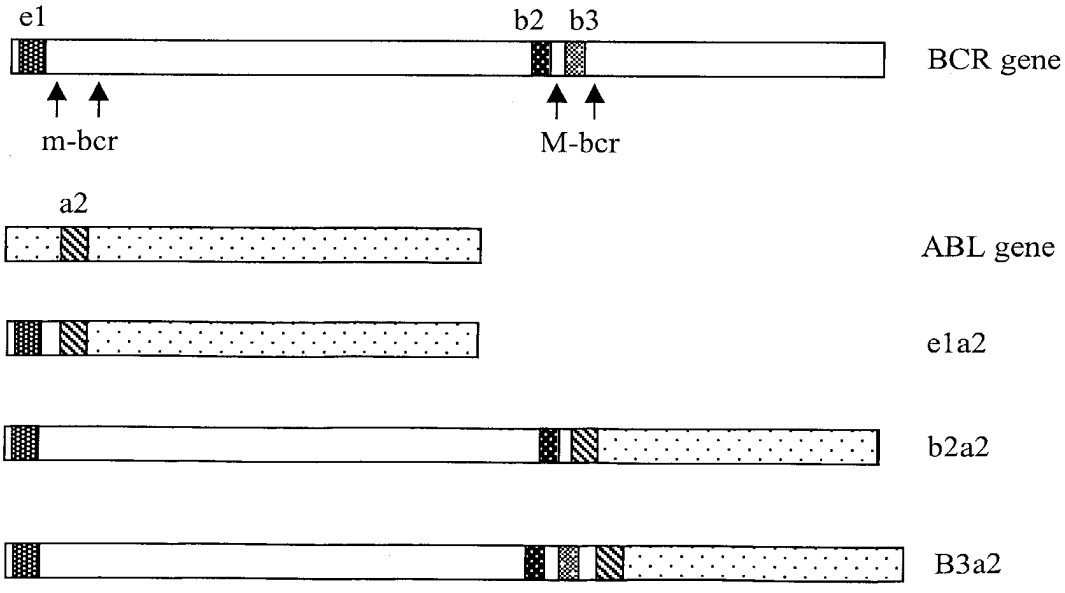
In accordance with 37 C.F.R. § 1.195, Appellants respectfully submit that good and sufficient reasons exist for the submission of Appellants' evidence subsequent to the final office action. Specifically, Appellants' submission was necessitated by the Examiner's failure to respond to a direct request for evidence supporting the asserted *prima facie* case, so that such evidence might be rebutted. Appellants could not be expected to provide rebuttal evidence earlier in prosecution in the absence of a clear understanding of the evidence on which the Examiner was relying. Once it was apparent that the Examiner would not present such evidence, Appellant made a submission of evidence in an effort to demonstrate the fallacy of the Examiner's unsupported assertions. Appellants respectfully request that the Board of Patent Appeals and Interferences consider the file history of the present application in its entirety, including the He *et al.*, Robertson and Walsh-Weller, and Kämpke *et al.* publications.

Summary of The Invention

The invention as presently claimed relates in part to assay methods for specifically detecting and/or quantifying BCR-ABL gene rearrangements. In particular, the presently claimed methods can provide highly reproducible qualitative and quantitative results in which the presence and/or amount of three different BCR-ABL translocations may be determined in a single assay.

Certain lymphoblastic diseases develop when two genes, BCR on chromosome 22 and ABL on chromosome 9, recombine to form a hybrid BCR-ABL gene with leukaemogenic properties. The mechanism which underlies this recombination is unknown, but additional chromosome sites may be involved to form complex BCR-ABL rearrangements. In most chronic

myeloid leukemias (CMLs), the BCR translocation region is known as the "major breakpoint cluster region" ("M-bcr"), and the resulting hybrid BCR-ABL genes typically comprise a "b2a2" or b3a2" junction, where the b2 or b3 region of BCR is joined to the a2 region of ABL. Similarly, in many acute lymphoblastic leukemias (ALLs), the BCR translocation region is known as the "minor breakpoint cluster region" ("m-bcr"), and the resulting hybrid BCR-ABL genes typically comprise an "e1a2" junction, where the e1 region of BCR is joined to the a2 region of ABL. Both CML and ALL are "clonal" diseases, meaning that single malignant progenitor cell proliferates into an abnormal population of cells, each containing an identical mutation. A schematic of the BCR and ABL genes, and the e1a2, b2a2 and b3a2 translocations, are as follows:



Analysis of these translocations may be performed using the "polymerase chain reaction," or "PCR," to amplify a nucleic acid of interest. PCR typically uses a pair of "primer" nucleic acids (referred to as a "forward" and a "reverse" primer) that flank the nucleic acid of interest, and which "prime" synthesis of a copy of the DNA between the probes when DNA polymerase is added. Following production of multiple copies of the target sequence, the copies are detected using labeled hybridization probes.

In the case of the present invention, a BCR e1 "forward" primer combines with an ABL a2 "reverse" primer to amplify a 219 base pair fragment if the e1a2 translocation is present; and a BCR b2/b3 forward primer combines with the same ABL a2 "reverse" primer to amplify a 124 base pair fragment if the b2a2 translocation is present, or a 199 base pair fragment if the b3a2 translocation is present. Detection of the amplification fragments is performed using two probes: 1 specific for the e1a2 translocation, and a second specific for the b2a2/b3a2 translocations. In addition, a GAPDH gene is also amplified using a primer pair and a specific probe. *See, e.g.*, specification, page 14 (describing the primers and probes), and page 28 (describing the fragments generated).

Thus, in the present invention, eight specific primers and probes (e1 forward, b2/b3 forward, a2 reverse, GAPDH forward, and GAPDH reverse primers; and e1a2, b2a2/b3a2, and GAPDH probes) set forth in SEQ ID Nos: 1-8 have been designed to differentiate between three BCR-ABL translocations, *i.e.*, e1a2, b2a2 and b3a2, in a single assay, as well as to provide an internal GAPDH control fragment. The primers and probes are designed for such a "multiplexed" analysis, where the skilled artisan will understand care must be taken to avoid spurious

"priming" of DNA synthesis by probe nucleic acids, primer/primer hybridization, primer/probe hybridization, etc. *See, e.g.*, specification, page 15, first paragraph. The methods for distinguishing all three BCR-ABL translocation rearrangements in a single assay comprise reverse transcribing the RNA to cDNA, amplifying the cDNA, and detecting a cDNA signal. In preferred embodiments, the amplification and detection of the cDNAs are accomplished by "Real Time PCR," which refers to specific PCR methods in which a signal emitted from the assay is monitored during the reaction as an indicator of amplicon production during each PCR amplification cycle (*i.e.*, in "real time").

As described in the specification on page 30, section 9.3.3, each BCR-ABL translocation provides an amplification product having a unique size. Figure 3 provides a visual demonstration of the ability of the present invention to detect each of these amplification products.

Issues

1. Whether claims 1-6 and 8-13, which refer to a method for determining BCR-ABL translocation rearrangements in a biological sample using each of the primers and probes set forth in SEQ ID NOS. 1-8, are unpatentable under 35 U.S.C. §103 (a) over Mansink *et al.*, in view of Hariharan *et al.* and further in view of Shtivelman.

2. Whether claims 1-13, which refer to a method for determining BCR-ABL translocation rearrangements in a biological sample using each of the primers and probes set forth in SEQ ID NOS. 1-8, are unpatentable under 35 U.S.C. §103 (a) over Eder *et al.*, in view of Hariharan *et al.* and further in view of Shtivelman and further in view of Ercolani *et al.*

3. Whether claims 2 and 3 which recite the phrase "real time PCR" meet the definiteness standard of 35 U.S.C. §112, second paragraph.

Grouping of Claims

Claims 1 and 4-12 stand or fall together; claims 2 and 3 stand or fall together, and claim 13 stands or falls alone.

Specifically, claims 1 and 4-12 refer to methods for determining BCR-ABL translocation rearrangements in a biological sample comprising a set of specific steps: extracting RNA, quantifying the RNA, reverse transcribing the RNA to cDNA, amplifying the cDNA and detecting the amplification products using the primers and probes of SEQ ID NOS. 1-8, obtaining a standard curve, and comparing the amplification results to the standard curve; claims 2 and 3 refer to these methods in which real time PCR is employed; and claim 13 refers to a method for determining BCR-ABL translocation rearrangements in a biological sample comprising amplifying and obtaining a signal from DNA using each of the primers and probes set forth in SEQ ID NOS. 1-8, wherein said DNA is obtained by reverse transcribing RNA obtained from said biological sample, and wherein said signal is indicative of the presence of BCR-ABL translocation rearrangements in said biological sample.

Argument

Appellants respectfully traverse the rejection of claims 1-6 and 8-13 under 35 U.S.C. 103 (a), as allegedly being unpatentable over Mansink *et al.*, in view of Hariharan *et al.* and further in view of Shtivelman; and of claims 1-13 under 35 U.S.C. 103 (a), as allegedly being unpatentable

over Eder *et al.*, in view of Hariharan *et al.* and further in view of Shtivelman and further in view of Ercolani *et al.*, because the Examiner's assertion that any and all primers from a known gene sequence would have an "expected functional equivalence" is unsupported by any evidence of record. Therefore, no *prima facie* case of obviousness has been established. Moreover, because the present claims refer to assays comprising 8 specific primers and probes that have been configured to differentiate each of the e1a2, b2a2 and b3a2 BCR-ABL rearrangements, a feature absent from any prior art document of record, any *prima facie* case of obviousness may have been established has been rebutted.

Appellants also respectfully traverse the rejection of claims 2 and 3 under 35 U.S.C. § 112, second paragraph, as allegedly being indefinite for failing to particularly point out and distinctly claim the present invention because of the recitation of the phrase "real time PCR" in the claims. Appellants respectfully submit that the phrase "real time PCR" is well known and used by the skilled artisan. In contrast, the Examiner's assertion that "all time is real time" represents an interpretation of the claims that fails to consider either the understanding of the skilled artisan as well as the clear definition provided by Appellants in the file history.

35 U.S.C. § 103

Appellants respectfully request that the rejections of claims 1-6 and 8-13 under 35 U.S.C. § 103(a) as allegedly being unpatentable over Mensink *et al.*, *British J. Haematol.* 102: 768-774 (1998) in view of Hariharan *et al.*, *EMBO J.* 6: 115-119 (1978) and further in view of Shtivelman, *Cell* 47: 277-284 (1986), and of claims 1-13 under under 35 U.S.C. § 103(a) as allegedly being unpatentable over Eder *et al.*, *Leukemia* 3: 1383-89 (1999) in view of Hariharan

et al. and Shtivelman, and in further view of Ercolani *et al.*, *J. Biol. Chem.* 263: 15335-15341 (1988) be withdrawn and reversed, as no *prima facie* obviousness has been established, or, in the alternative, any *prima facie* case of obviousness has been rebutted.

Applicable Legal Standard

To establish a *prima facie* case of obviousness, three criteria must be met: there must be some motivation or suggestion, either in the cited references or in knowledge available to the ordinarily skilled artisan, to modify or combine the references; there must be a reasonable expectation of success in combining the references; and the references must teach or suggest all of the claim limitations. *In re Vaeck*, 20 USPQ2d 1438 (Fed. Cir. 1991) *See also,* MPEP §2143.

The cited references, alone or in combination, do not disclose any methods using the eight primers and probes of the present claims, which are able to differentiate three BCR-ABL translocations

As Appellants stated in the foregoing "Summary of the Invention," the instant claims refer to methods employing a set of eight specific primers and probes. These nucleic acids have been selected to differentiate the presence of the e1a2, b2a2 and b3a2 BCR-ABL translocations in a single, multiplexed assay.

In contrast, the primary Mensink *et al.* publication discloses a method for quantitation of a single BCR-ABL cDNA fragment using only a single primer pair and a single probe that are designed to detect only the b2a2 and b3a2 BCR-ABL translocations. *See, e.g.*, Mensink *et al.*, page 769, right column, second and third full paragraphs; and page 773, left column, 23-25 ("The PCR primers were located in exon BCR2 and ABL exon 2. This enabled detection and quantitation of the most common B2A2 and B3A2 fusion transcripts"). The Examiner does not

assert that the primer pair and probe disclosed in the Mensink *et al.* publication are identical to any of the primers and probes of the present claims, much less that the Mensink *et al.* publication discloses any assays capable of differentiating each of the e1a2, b2a2 and b3a2 BCR-ABL translocations.

Similarly, the primary Eder *et al.* publication discloses a method for quantitation of only the b2a2 and b3a2 variants of BCR-ABL, in this case using two pairs of primers and two probes. *See, e.g*, Eder *et al.*, abstract. Again, the Examiner does not assert that the primer pairs and probes disclosed in the Eder *et al.* publication are identical to any of the primers and probes of the present claims, much less that the Eder *et al.* publication discloses any assays capable of differentiating each of the e1a2, b2a2 and b3a2 BCR-ABL translocations.

The Examiner has not met the initial burden required to combine the publications as suggested, thereby failing to establish a prima facie case of obviousness

Because the primary Mensink *et al.* and Eder *et al.* publications do not themselves disclose or suggest the instantly claimed invention, the Examiner seeks to combine each of the primary publications with the secondary the Hariharan *et al.* and Shtivelman publications, which are cited as simply disclosing the complete DNA sequences of BCR and ABL, respectively. The Examiner contends that "the only significant difference between the prior art and the current claims is the particular primers selected from the BCR and from the ABL sequences" (Paper No. 14, page 12), and that the primers of the claims "simply represent structural homologs" of the primers in the Mensink *et al.* and Eder *et al.* publications (*id.*, page 6) which may be obtained from the complete BCR and ABL sequences. The Ercolani *et al.* publication is cited by the

Examiner solely for the disclosure of a full length GAPDH sequence. *See, e.g.*, Paper No. 14, page 10.

Applicants respectfully submit that it is the Examiner's initial burden to establish a *prima facie* case of obviousness, and unsupported assertions that the primers of the claims "simply represent structural homologs" of the primers in the primary publications do not meet this burden. The Court of Appeals for the Federal Circuit has repeatedly cautioned that:

> [t]he factual inquiry whether to combine references of record must be thorough and searching. It must be based upon objective evidence of record.... [T]he best defense against the subtle but powerful attraction of a hindsight-based obviousness analysis is rigorous application of the requirement for a showing of the teaching or motivation to combine prior art references.... [P]articular findings must be made as to the reason the skilled artisan, with no knowledge of the claimed invention, would have selected these components for combination in the manner claimed.

In re Sang-Su Lee, 277 F.3d 1338, 1343 (2002) (internal citations omitted, emphasis added).

As Appellants previously noted, there is nothing supporting the obviousness rejection other than the Examiner's bare assertions that the primers referred to in the instant claims are "structural homologues" of the primers disclosed in the primary publications. Appellants further noted that, while the individual nucleotides making up typical nucleic acids are chosen from the same "alphabet" of A, T, G, and C, the relative arrangement of nucleotides provides unique structural and functional properties to any particular nucleic acid that are not "homologous" to other nucleic acids having a different arrangement of nucleotides. Appellants respectfully submit that nothing of record indicates a reasonable expectation that nucleic acids having different sequences will have similar properties; hence, no presumption of obviousness based on structural similarity is permitted. *See*, MPEP § 2144.09.

Likewise, the Examiner's erroneous conclusion that "[a]n ordinary practitioner would expect successful detection of the BCR-ABL translocation from every primer selected according to the methodology taught by Eder" (Paper No. 14, page 12), is unsupported by any objective evidence and is, in fact, contrary to the understanding of those skilled in the art. Rather, the skilled artisan is well aware that each potential primer in a given nucleic acid sequence is not structurally or functionally equivalent. Taken to its logical conclusion, the Examiner's position renders any of the many thousands of potential primer sequences that might be obtained from a large nucleic acid molecule automatically *prima facie* obvious, without any need to provide evidence that any particular sequence will function as a primer at all.

In response to the first office action, Appellants' explicitly requested that the Examiner provide some objective evidence in support of the assertions made in the rejection, so that the evidence might be considered and rebutted. In response, the Examiner offered only additional unsupported assertions. For example, the Examiner's assertion that "[t]he primers are all drawn from the identical sequence for the identical purpose, so an ordinary practitioner would have been motivated to select primers using software expressly disclosed by Mensink, the Primer Express software, where the software selects primers based on input criteria of desired Tm, length, and other well known parameters" (Paper No. 17, page 2, first full paragraph) is not obtained from the prior art, but merely springs from the Examiner's pen. The Examiner continues to ignore the need for particular findings, based on evidence of record, as to the reason the skilled artisan, with no knowledge of the claimed invention, would have selected these components for combination in the manner claimed. Moreover, the Examiner's assertion of

"identical purpose" is clearly wrong, as the sequences of the present claims are selected to detect each of the e1a2, b2a2 and b3a2 BCR-ABL translocations, while the sequences of the Mensink *et al.* and Eder *et al.* publications are not. *See, e.g.*, specification, page 15, first paragraph.

Appellants respectfully submit that, because the Examiner has failed to perform the thorough and searching factual inquiry necessary to support an assertion of obviousness, or based the rejection upon any objective evidence of record, the Examiner has failed to meet the burden of establishing a *prima facie* case of obviousness. Instead of analyzing the scope and content of the prior art, the level of skill in the art, the differences between the claimed invention and the prior art, and any objective indicia of non-obviousness, the Examiner has sought to short-circuit the inquiry by simply asserting "[a]n ordinary practitioner would expect successful detection of the BCR-ABL translocation from every primer selected," without objective support for such a statement. Paper No. 14, page 12.

Rather than consider the scope and content of the prior art, the Examiner has relied on unsupported opinion in the obviousness rejection

As noted above, the Examiner failed, despite Appellants' explicit request, to provide any objective evidence in support of the obviousness rejection. In spite of the fact that it is the Examiner's burden to establish a *prima facie* case of obviousness, and not the applicant's burden to prove non-obviousness, Appellants attempted to educate the Examiner concerning the fallacy of the position that all possible primers from a large sequence "simply represent structural homologs" of all other possible primers obtained from such a sequence.

Rather than consider the evidence provided by Appellants, which was well known in the art, the Examiner contends that these citations are allegedly inappropriate and untimely, since the references were only cited in prosecution following the issuance of a final office action. Paper No. 17, page 2, third full paragraph. Appellants respectfully submit that, in refusing to consider Appellants' evidence, the Examiner has lost sight of "the importance of his or her role in allowing claims which properly define the invention." MPEP § 706. Appellants further submit that the Examiner's decision to not consider this evidence is emblematic of the Examiner's failure to consider fully the scope and content of the prior art, as required in any obviousness analysis.

As noted above in the "Status of Amendments" section of this Brief, and in accordance with 37 C.F.R. § 1.195, Appellants respectfully submit that good and sufficient reasons exist for the submission of Appellants' evidence subsequent to the final office action, and Appellants respectfully request that the Board of Patent Appeals and Interferences consider the file history of the present application in its entirety, including the He *et al.*, Robertson and Walsh-Weller, and Kämpke *et al.* publications.

In this regard, Appellants submitted He *et al.*, *BioTechniques* 17: 82-87 (1994), which notes that primers that differ even "slightly" in position can exhibit 100- to 1000-fold differences in amplification sensitivity, and that "a trial-and-error" approach must be used to identify useful primers. He *et al.*, abstract. Similarly, Appellants submitted an excerpt from Robertson and Walsh-Weller, *Meth. Mol. Biol.* 98: 121-126 (1998), which confirms that, simply because a computer program is used to select sets of primers, the skilled artisan would not expect every primer set to be either structurally or functionally homologous. *See, e.g.*, Robertson and Walsh-

Weller, pages 122-123 (while "there are guidelines, as reported by numerous authors, that may be useful in designing effective primers... [d]espite a gallant attempt at optimization of the PCR and primer design, poor sensitivity might only be relieved when new primer pairs are tried") (citing He *et al.*).

Furthermore, the Robertson and Walsh-Weller publication also cautions on page 124 that the results obtained from primer design software, such as that allegedly disclosed by the Eder *et al.* publication, must be "regard[ed]... with healthy skepticism." Current software algorithms suffer from the fact that "important factors which influence the stability of nucleic acids have yet to be identified." Kämpke *et al.*, Bioinformatics 17: 214-25 (2001), page 224, right column. This is particularly true in multiplex PCR assays, such as those of the instant claims. See, e.g., *id.*, page 214, right column ("The design complexity increases in so-called multiplex PCR.... [T]his requires that physical parameters such as cycle number, cycle duration and annealing temperature are identical for all of the PCR reactions. Moreover, the analysis of unintended primer-primer interactions becomes more intricate"). As a result, "a trial-and-error" approach continues to be required to obtain useful primers, particularly for multiplex primer sets.

When properly considered, it is apparent that the skilled artisan would clearly not expect successful detection of the BCR-ABL translocation from every primer selected from a particular sequence. It is equally apparent that the skilled artisan would not consider the primers referred to in the instant claims, which can provide highly reproducible qualitative and quantitative results in which the presence and/or amount of three different BCR-ABL translocations, "structural homologues" of the primers disclosed in the cited publications. When the scope and

content of the prior art is properly considered, it is clear that the Examiner's unsupported reasoning in support of the obviousness rejection is incorrect. Thus, Appellants respectfully submit that no *prima facie* case of obviousness has been established.

The superior properties of the claimed invention overcome any prima facie case of obviousness that may have been established

It is also respectfully submitted that the methods of the instant claims, which recite the use of 8 specifically designed nucleic acid primers and probes, provide methods by which the presence and/or amount of three different BCR-ABL translocations may be distinguished in a single assay. As described in the specification on page 30, section 9.3.3, each of the e1a2, b2a2 and b3a2 BCR-ABL translocations for which the primers and probes of the present claims have been designed provides an amplification product having a unique size when amplified according to the claimed methods. Figure 3 provides a visual demonstration of the ability of the present invention to detect each of these amplification products.

In contrast, the cited Mensink *et al.* publication discloses one primer pair and one probe for detection only the b2a2 and b3a2 translocations, while the Eder *et al.* publication discloses two primer pairs and two probes for detection of these same translocations. *See, e.g.*, Mensink *et al.*, page page 773, left column, 23-25 ("The PCR primers were located in exon BCR2 and ABL exon 2. This enabled detection and quantitation of the most common B2A2 and B3A2 fusion transcripts"); Eder *et al.*, abstract. Because none of the publications cited by the Examiner detects each of the e1a2, b2a2 and b3a2 BCR-ABL translocations in a single assay, the methods of the instant claims provide superior results as compared to the cited publications. To the extent that a

prima facie case of obviousness has been established, such a *prima facie* case is rebutted by this evidence of superior results. *See, e.g.*, MPEP §2144.09.

In response to Appellants' evidence in this regard, the Examiner asserts that "applicant's statement is not evidence and the specification lacks comparative data," and that these arguments are simply the "arguments of counsel." Paper No. 14, page 12. Appellants respectfully disagree with this characterization. The instant specification describes in detail the claimed methods "designed to be able to amplify and detect all three translocations of the BCR-ABL gene, namely e1a1, ba2a2, and b3a2, without interfering with each other and providing highly reproducible results." Specification, page 15, first paragraph. The comparative data of record is provided by the specification, together with the fact that no publications of record provide any such assays. The Examiner must consider such data in the specification. *See, e.g.*, MPEP § 716.01(a).

Furthermore, while the Examiner contends that "use of the cited prior art method itself in separate experiments might yield equally effective data" (Paper No. 14, page 12), Appellants are not required to compare the claimed invention with subject matter that does not exist in the prior art. *See, e.g.*, MPEP § 716.02(e). Moreover, it is plain on the face of the Mensink *et al.* publication that only one primer pair and one probe is disclosed which, because of their position in the BCR and ABL genes, could not differentiate each of the e1a2, b2a2 and b3a2 BCR-ABL translocations. Likewise, it is equally plain on the face of the Eder *et al.* publication that only two primer pairs and two probes are disclosed which, because of the size of the amplicons generated by these primers, could not differentiate each of the e1a2, b2a2 and b3a2 BCR-ABL translocations. Eder *et al.*, page 1384, right column, final paragraph. The assertion that such

methods could possibly distinguish each of the e1a2, b2a2 and b3a2 BCR-ABL translocations is scientifically unsupportable.

Because no *prima facie* case of obviousness has been established, or, in the alternative, any *prima facie* case of obviousness that may have been established has been rebutted, Appellants respectfully request that the rejection under 35 U.S.C. §103 (a) be withdrawn or reversed.

35 U.S.C § 112, 2nd Paragraph

Appellants respectfully request that the rejection of claims 2 and 3 under 35 U.S.C. §112, second paragraph be withdrawn and reversed. Appellants submit that because the skilled artisan is reasonably apprised of the meaning of this phrase "real time PCR," Claims 2 and 3 are not indefinite with the meaning of 35 U.S.C. §112, second paragraph.

Applicable Legal Standard

When determining definiteness, the proper standard to be applied is "whether one skilled in the art would understand the bounds of the claim when read in the light of the specification." *Credle v. Bond*, 30 USPQ2d 1911, 1919 (Fed.Cir.1994). See also *Miles Laboratories, Inc. v. Shandon, Inc.*, 27 USPQ2d 1123, 1127 (Fed.Cir.1993) ("If the claims read in the light of the specification reasonably apprise those skilled in the art of the scope of the invention, § 112 demands no more.").

The term "Real Time PCR" is well known and accepted by those of skill in the art

Appellants respectfully disagree with the Examiner's assertion that the phrase "real time PCR" in claims 2 and 3 is allegedly indefinite as "all PCR amplification reactions are conducted in real, as opposed to imaginary time." Paper No. 14, page 2. The phrase "real time PCR" is well known to those of skill in the art as referring to specific PCR methods in which a signal emitted from the assay is monitored during the reaction as an indicator of amplicon production during each PCR amplification cycle (*i.e.*, in "real time"), as opposed to conventional PCR methods, in which an assay signal is detected at the endpoint of the PCR reaction. Appellants respectfully submit that, from the point of view of the skilled artisan, the phrase "real time PCR" is both well known and commonly used. As an indication of the acceptance of this phrase by those of skill in the art, Appellants provided the partial results of a search of the *Medline* database, which revealed 383 publications in which the term is used in the title. *See, e.g.*, Appellants' response to the first office action.

As stated in MPEP §2173.02, "[d]efiniteness of claim language must be analyzed, not in a vacuum, but in light of... [t]he teachings of the prior art; and [t]he claim interpretation that would be given by one possessing the ordinary level of skill in the pertinent art at the time the invention was made." The Examiner's discussion of "imaginary time" is not based on any analysis of the phrase from the point of view of the artisan, but is instead an interpretation of the phrase that is uninformed by the knowledge with which those of skill in the art would interpret the phrase. The Examiner's failure to properly analyze the claims renders the Examiner's allegation of indefinitess fatally flawed.

Indeed, the Examiner agrees that the phrase "real time PCR" is used in numerous publications by artisans, *e.g.*, in 213 publications according to the Examiner's search. The Examiner, however, rather than acknowledging that this common usage that the skilled artisan clearly understand the metes and bounds of the phrase, argues that "these papers do not use the term to mean the same thing," and refers in particular to the protocols and instruments disclosed in two of the publications, *i.e.*, Dehèe *et al.* and Aldea *et al.* publications. Paper No. 14, page 11. It is respectfully submitted that whether or not different protocols and instruments are used in performing real time PCR is irrelevant to whether or not the skilled artisan is reasonably informed of the metes and bounds of claims using the phrase "real time PCR." Just as the skilled artisan understands the meaning of the term "PCR" (or "centrifugation," or "ion exchange chromatography," or any of other myriad techniques commonly used in the art) regardless of the particular protocol employed or apparatus used, the two publications to which the Examiner refers indicate that the skilled artisan clearly understands the phrase "real time PCR" regardless of the particular protocol employed.

For example, the Dehée *et al.* publication cited by the Examiner discloses the use of the commercially available "Taqman" system in real time PCR, and describes real time PCR as follows: "during each PCR cycle one molecule of reporter dye is cleaved for each target molecule amplified. The released reporter fluorescence is measured in real time." Dehée *et al.*, page 39, right column, last paragraph. Similarly, the Aldea *et al.* publication cited by the Examiner uses a different commercially available system, referred to as "LightCycler," for precisely the same purpose. The Aldea *et al.* publication states in the first paragraph that "real-

time PCR has started to demonstrate its potential utility.... The main features making this new technology so attractively suitable for these applications, in comparison to conventional PCR, are rapidness, possibility of accurate quantification, and... reduction of likelihood of contamination, since no postamplification analysis of the tubes is required."

It is respectfully submitted that both Dehèe *et al.* and Aldea *et al.* publications confirm that the phrase "real time PCR" as used in the art refers to a PCR method in which a signal emitted from the assay is monitored during the reaction as an indicator of amplicon production during each PCR amplification cycle, as opposed to conventional PCR methods, in which an assay signal is detected at the endpoint of the PCR reaction. The fact that the authors of the publications cited by the Examiner use different protocols and instruments, but still recognize that each is using "real time PCR," supports the conclusion that the skilled artisan is reasonably informed of the metes and bounds of the phrase "real time PCR."

Moreover, if any latent ambiguity remains in the phrase, Appellants have clearly indicated that the meaning of the phrase "real time PCR" for purposes of the present application corresponds to its well established meaning in the relevant art. Thus, the skilled artisan is reasonably informed of the meaning of the phrase as used in the instant claims.

Appellants respectfully submit that, because the phrase "real time PCR" is commonly understood by those of ordinary skill in the art, and because Appellants have made clear that this commonly understood meaning applies to the phrase "real time PCR" as used in the instant claims, the skilled artisan is reasonably apprised of the scope of the present claims. 35 U.S.C. §112, second paragraph, demands no more. Because the claims, when properly interpreted, meet

the standards of 35 U.S.C. §112, second paragraph, Appellants respectfully request that the rejection be withdrawn or reversed.

Conclusion

For the reasons discussed above, the instant claims are in condition for allowance, and Appellants respectfully request that the rejections be withdrawn or reversed, and that the claims be allowed to issue.

Respectfully submitted,

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Appendix A: Text of the Claims Involved in the Appeal

1. A method for determining BCR-ABL translocation rearrangements in a biological sample comprising the steps of:

a) extracting RNA from a biological sample;

b) quantifying the extracted RNA;

c) reverse transcribing the RNA to cDNA;

d) amplifying the cDNA and detecting a cDNA signal by using each of the primers and probes set forth in SEQ. ID NOS. 1-8;

e) obtaining a standard curve of cDNA signals from serial dilutions of a leukemic cell line, wherein the cDNA is obtained by repeating steps a) – d) with the RNA from leukemic cell line and not the sample; and

f) extrapolating a measurement of the leukemic cells present in the sample by comparing the signal from step d) with that from step e).

2. The method of claim 1 wherein the amplification and detection of the cDNA is step d) is accomplished by Real Time PCR.

3. The method of claim 1 wherein the amplification and detection of the cDNA in step e) is accomplished by Real Time PCR.

4. The method of claim 1 wherein the measurement in step f) comprises a measurement of the number of leukemic cells present in the sample, wherein a result of less than a certain number of cells is reported as negative, and a result of more than a certain number is reported as positive.

5. The method of claim 4 wherein wherein a result of less than one leukemic cell per ten thousand total cells is reported as negative, and a result of more than one leukemic cell per ten thousand total cells is reported as positive.

6. The method of claim 1 wherein the measurement in step f) comprises measurement of the total number of leukemic cells present in the sample.

7. The method of claim 1 further comprising the step of running the cDNA PCR products of step d) on an electrophoretic gel to obtain fragment size and hence identity information.

8. The method of claim 1 wherein the amplification and detection of the cDNA in step d) is performed in a single container.

9. The method of claim 1 wherein the amplification and detection of the cDNA in step e) is performed in single container.

10. A method of diagnosing CML or ALL by performing the assay of claim 1.

11. A method of diagnosing CML or ALL by performing the assay of claim 7.

12. The method of claim 1 wherein the sample includes an RNAse inhibitor.

13. A method for determining BCR-ABL translocation rearrangements in a biological sample, the method comprising:

amplifying and obtaining a signal from DNA using each of the primers and probes set forth in SEQ ID NOS. 1-8, wherein said DNA is obtained by reverse transcribing RNA obtained from said biological sample, and wherein said signal is indicative of the presence of BCR-ABL translocation rearrangements in said biological sample.